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(19)

(54) NEW TETRAHYDROCARBAZOLE DERIVATIVES AND PROCESS FOR THEIR MANUFACTURE

(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby

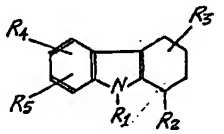
declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new tetrahydrocarbazole derivatives, with a process for their manufacture and with their use.

From German Offenlegungsschrift No. 2,042,280 it has been known that N - alkyl-1,2,3,4 - tetrahydrocarbazoles substituted in the 4-position by aminoalkyl groups possess a hypoglycaemic action.

It has now been found that tetrahydrocarbazoles substituted in the 1-position possess, at a low toxicity, a considerably stronger blood sugar-lowering action and also antifungal, fertility-inhibiting and anti-inflammatory properties.

The present invention accordingly provides compounds of the general formula I



(I)

R_1 represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms,

R_2 represents a hydroxyalkyl, aminoalkyl, acetamidoalkyl, azidoalkyl or a tosyloxyalkyl group containing 1 to 4 carbon atoms in the alkyl group and, when R_1, R_3, R_4 and R_5 are not all simultaneously hydrogen atoms, may also represent a group of the general formula

$$-(CH_2)_n-X,$$

in which n represents 0 or 1 and X represents a carboxyl, alkoxycarbonyl, carbamoyl or nitrile group,

R_3 represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms, and

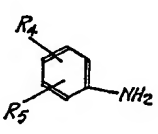
R_4 represents a hydrogen or fluorine atom, an alkyl group containing 2 to 6 carbon atoms, a trifluoromethyl group, an alkoxy group containing 3 to 6 carbon atoms, or a nitro, carboxyl, amino, hydroxyl or nitrile group and, when R_5 does not represent a hydrogen atom, may also represent a chlorine atom, and

R_5 represents in the 5-, 7- or 8-position a hydrogen atom, a halogen atom, an alkyl group containing 1 to 4 carbon atoms, an alkoxy group containing 1 to 6 carbon atoms, or

R_4 and R_5 together represent a 6,7 - methylene dioxy group, and also their enantiomers and, when the compounds are capable of forming salts, salts thereof with inorganic or organic acids or bases.

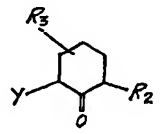
The present invention also provides a process for the manufacture of the aforesaid new compounds of the present invention, wherein

a) a substituted aniline of the general formula II



(II),

in which R_4 and R_5 have the meanings given above, or a salt thereof, is reacted with a cyclohexanone derivative of the general formula III



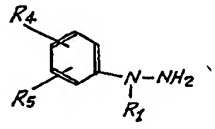
(III),

in which R_2 represents a

$$-(CH_2)_n-X$$

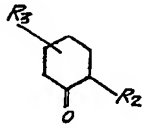
group in which n and X have the meanings given above, Y represents a halogen atom, preferably a bromine atom, and R_3 has the meaning given above, and, if desired, the resulting compound is alkylated at the nitrogen atom in a manner known *per se* to form a compound in which R_1 represents an alkyl group containing 1 to 4 carbon atoms, or

b) an N_1-substituted phenyl - hydrazine of the general formula IV



(IV),

in which R_1, R_4 and R_5 have the meanings given above, or a salt thereof, is reacted with a cyclohexanone derivative of the general formula V



(V),

in which R_2 and R_3 have the meanings given above, if desired, any resulting acid derivative obtained according to method (a) or (b) is hydrolysed and/or any resulting free 1 - carboxylic acid is converted into an ester thereof, and/or if desired, any resulting ester is either (i) converted in a manner known *per se* into a carbamoyl compound and then, if desired, the carbamoyl compound is reduced to an aminoalkyl compound or (ii) reduced in a manner known *per se* to a hydroxyalkyl compound, the hydroxyalkyl compound is then, if desired, converted into the tosylate, the tosylate is then, if desired, converted into an azidoalkyl compound and the azidoalkyl compound is, if desired, reduced to an aminoalkyl compound, and/or, if desired, any resulting compound capable of forming a salt is converted into a salt thereof and/or any resulting salt is converted into the corresponding free compound.

In the reaction according to method (a) the substituted aniline is advantageously present in excess, and preferably in a 2.2 to 2.5 molar excess. The reaction may be carried out with or without solvents. As solvents there are preferably used alcohols, for example ethanol and butanol, or ethers, for example dioxan and dimethoxyethane. In working without a solvent an excess of the aniline component may be used as solvent. In both cases there may be used a catalyst, for example zinc chloride.

The reaction is preferably carried out in an atmosphere of a protective gas, for example an atmosphere of nitrogen or a rare gas.

The reaction temperature depends on the choice of the solvent and is within the range of from 80 to 200°C; it is preferably within the range of from 140 to 150°C, above all when working without a solvent or when solid aniline components are used.

The reaction is carried out under atmospheric pressure or reduced pressure, preferably at 100 mm of mercury.

The reaction according to method (b) is carried out at temperatures within the range of from 50 to 150°C and may be carried out with or without a solvent with the use of catalysts known for the Fischer-indole synthesis, for example $ZnCl_2$, HCl, H_2SO_4, phosphoric acid, polyphosphoric acid and BF_3. As solvents there are preferred glacial acetic acid, acetic acid and alcohols. The reaction may, however, be carried out without a solvent in molten zinc chloride or in polyphosphoric acid and phosphoric acid.

The compounds of the present invention possess valuable pharmacological properties. For example, they exhibit a superior blood sugar-lowering action coupled with a markedly lower toxicity, which is an especially important property for a therapeutic agent having a long period of action. In the following Table there are given the values for the blood sugar-lowering action of a few compounds of the present invention as compared with 4 - aminomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole (cf. German Offenlegungsschrift No. 2,042,280).

TABLE

Substance	Dose mg/kg	Blood sugar (% of the initial value) 1.5 hours	3 hours
4 - Aminomethyl - 9 - methyl - 1,2, 3,4 - tetrahydrocarbazole hydrochloride (DOS 2,042,280)	50	88.5+	87.0+
	250	64.0	60.0
1 - Carboxy - 6 - fluoro - 1,2,3,4-tetrahydrocarbazole	50	59.5	67.5
	250	33.0	30.0
1 - Carboxy - 7 - fluoro - 1,2,3,4-tetrahydrocarbazole	50	71.5+	70.5+
	250	41.0	37.0
1 - Carboxymethyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole	50	63.5	72.0
	250	47.5	48.0

+ This value is not significant

$P \leq 0.05$ different from the control value.

The blood sugar values are expressed as a percentage of the initial concentration of blood sugar in adrenalectomised rats fasted for 24 hours, after oral administration of the substance in microsuspension. They are the mean values of groups of animals, each consisting of 6 rats, of which the initial blood sugar value and the blood sugar values after 90 and 180 minutes were determined.

The compounds exhibit a remarkably low toxicity, which is an especially important property for a therapeutic agent having a long period of action, such as a blood sugar-lowering agent. Thus, the LD_{50}-value of 1 - carboxy - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole is 1.5 g/kg, as determined upon male mice (NMRI-mice, fed) by the method of Kärber (cf. L. Ther. Grundlagen der experimentellen Arzneimittelforschung, Wiss. Verlagsgesellschaft Stuttgart, 1965, pages 77—79), the compound being administered in microsuspension orally to groups each containing 3 mice.

It will be seen from the Table that the compounds of the present invention exhibit a substantially stronger blood sugar-lowering activity than the amine tested for comparison. Accordingly, the compounds of the invention are potent pharmaceutical agents for the treatment of Diabetes mellitus. For this purpose the compounds may be administered, when they are capable of salt formation, in the form of physiologically tolerable salts with inorganic or organic bases, for example as salts of alkali and alkaline earth metal hydroxides or of amines, for example methylglucamine, morpholine or ethanolamine, or in the form of physiologically tolerable salts with inorganic or organic acids, for example hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, methane sulphonic acid, para - toluene sulphonic acid, naphthalene - 1,5 - disulphonic acid, acetic acid, lactic acid, succinic acid, tartaric acid, maleic acid or nicotinic acid.

For therapeutic use the substances may be administered alone or in admixture with suitable carrier substances, taste correctives or other additions normally used in galenical pharmacy.

The present invention accordingly further provides a pharmaceutical preparation which comprises a compound of the general formula I or an enantiomer thereof or a physiologically tolerable salt of either such compound capable of forming a salt in admixture or conjunction with a pharmaceutically suitable carrier.

The pharmaceutical preparations may be, for example, in powdered form, for example as tablets, dragées, capsules or pills, or in the form of suspensions or solutions.

The comounds of the invention also exhibit antifungal, anti-inflammatory and fertility-inhibiting activity.

The following Examples illustrate the invention:

Example 1

1 - Ethoxycarbonyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole

10 grams of 3 - bromo - 2 - oxo - cyclohexane carboxylic acid ethyl ester were mixed with 10 grams of para - fluoraniline and heated for 5 hours at 140°C while stirring, the pressure being maintained at 100 mm of mercury. When the mixture had cooled it was diluted with carbon tetrachloride, the undissolved precipitate was filtered off, and the organic phase was washed first with water and then with dilute hydrochloric acid. After drying the organic phase with magnesium sulphate, the solvent was distilled off *in vacuo*, and the residue was chromatographed over silica gel with a mixture of benzene and cyclohexane.

Yield: 60% of the theoretical yield of oily 1 - ethoxycarbonyl - 6 - fluoro - 1,2, 3,4 - tetrahydrocarbazole.

The structure of the oily product was confirmed spectroscopically.

Example 2

1 - Ethoxycarbonyl - 6 - trifluoromethyl - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 3 - bromo - 2 - oxo - cyclohexane carboxylic acid ethyl ester and 4 - trifluoromethyl - aniline in a manner analogous to that described in Example 1.

Yield: 30% of the theoretical yield of 1 - ethoxycarbonyl - 6 - trifluoro - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 94°C (benzine).

Example 3

1 - Ethoxycarbonyl - 6 - *n* - butyl - 1,2,3,4-tetrahydrocarbazole

The preparation was carried out from 4 - *n* - butyl - aniline and 3 - bromo - 2 - oxo-cyclohexane carboxylic acid ethyl ester in a manner analogous to that described in Example 1.

Yield: 61% of the theoretical yield of oily 1 - ethoxycarbonyl - 6 - *n* - butyl - 1,2,3,4 - tetrahydrocarbazole.

The structure of the oily product was confirmed spectroscopically.

Example 4

1 - Ethoxycarbonyl - 6 - nitro - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 4 - nitroaniline and 3 - bromo - 2 - oxo - cyclohexane carboxylic acid ethyl ester by heating them for 7 hours in a manner analogous to that described in Example 1.

Yield: 10% of the theoretical yield of 1 - ethoxycarbonyl - 6 - nitro - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 131°C (methanol).

Example 5

1 - Ethoxycarbonyl - 7 - fluoro - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 3 - bromo - 2 - oxo - cyclohexane carboxylic acid ethyl ester and 3 - fluoraniline by heating them for 7 hours in a manner analogous to that described in Example 1.

Yield: 32% of the theoretical yield of 1 - ethoxycarbonyl - 7 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 49°C (a mixture of ether and benzine).

Example 6

1 - Ethoxycarbonyl - 5 - chloro - 8 - methoxy - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 3 - bromo - 2 - oxo - cyclohexane carboxylic acid ethyl ester and 5 - chloro - 2 - methoxyaniline in a manner analogous to that described in Example 1. After heating the mixture for 2 hours at 140°C, zinc chloride was added as catalyst, and the whole was heated for a further 5 hours. Working up was then carried out in a manner analogous to that described in Example 1.

Yield: 25% of the theoretical yield of 1 - ethoxycarbonyl - 5 - chloro - 8 - methoxy-1,2,3,4 - tetrahydrocarbazole.

Melting point: 88°C (cyclohexane).

Example 7

1 - Ethoxycarbonyl - 6,7 - methylenedioxy-1,2,3,4 - tetrahydrocarbazole

10 grams of 3 - bromo - 2 - oxo - cyclohexane carboxylic acid ethyl ester were dissolved in 100 ml of absolute ethanol, and 11 grams of 3,4 - methylenedioxy - aniline were added to the solution. The reaction mixture was boiled under reflux for 2 hours in an atmosphere of nitrogen, then 0.5 gram of zinc chloride was added, and the whole was boiled under reflux for a further 3 hours. The greater part of the solvent was then distilled off *in vacuo*, and the residue was taken up in carbon tetrachloride. Undissolved 3,4 - methylenedioxy - aniline hydrobromide was removed, and the organic phase was washed with water, dried with magnesium sulphate, and concentrated *in vacuo*. The residue was purified chromatographically over silica gel with a mixture of benzene and chloroform.

Yield: 40% of the theoretical yield of oily 1 - ethoxycarbonyl - 6,7 - methylenedioxy - 1,2,3,4 - tetrahydrocarbazole.

The structure of the oily product was confirmed spectroscopically.

Example 8

1 - Ethoxycarbonyl - 6 - fluoro - 3 - methyl 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 4 - fluoraniline and 3 - bromo - 5 - methyl - 2 - oxo - cyclohexane carboxylic acid ethyl ester in a manner analogous to that described in Example 1.

Yield: 65% of the theoretical yield of oily 1 - ethoxycarbonyl - 6 - fluoro - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole.

The structure of the oily product was confirmed spectroscopically.

The preparation of 3 - bromo - 5 - methyl-2 - oxo - cyclohexane carboxylic acid ethyl

ester was carried out in the following manner:

40 grams of 5 - methyl - 2 - oxo - cyclohexane carboxylic acid ethyl ester and 96 grams of cupric bromide were boiled under reflux for 3 hours in a mixture of 80 ml of chloroform/ethyl acetate (1:1) for 3 hours under reflux. When the black-green colouration had disappeared, the white precipitate (Cu_2Br_2) was filtered off and washed with chloroform, and the combined filtrates were washed with water. The solvent was then removed *in vacuo*. The resulting oil was used in the above reaction.

Example 9

1 - Ethoxycarbonyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole

23.5 grams of cyclohexanone - 2 - carboxylic acid ethyl ester were dissolved in 300 ml of absolute ethanol, and 21.9 grams of 1 - methyl - 1 - phenyl - hydrazine hydrochloride were added. The solution was boiled under reflux for 5 hours, then concentrated *in vacuo*, taken up in methylene chloride and washed with water. The organic phase was dried over magnesium sulphate, the solvent was removed *in vacuo*, and the residue was chromatographed over silica gel with a mixture of benzene and cyclohexane.

Yield: 70% of the theoretical yield of 1 - ethoxycarbonyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

The structure of the oily product was confirmed spectroscopically.

Example 10

1 - Cyanomethyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole

15 grams of 2 - cyanomethyl - cyclohexanone were heated with 17.8 grams of 4 - fluorophenyl - hydrazine hydrochloride in 110 ml of water for 10 minutes on a steam bath. Then 170 ml of glacial acetic acid were added and the whole was heated for a further 40 minutes. When it had cooled the solution was cautiously buffered with sodium carbonate and extracted several times with ether. After drying the combined ether phases, they were concentrated *in vacuo*, and the residue was chromatographed over silica gel, and then recrystallized twice from ether.

Yield: 15% of the theoretical yield of 1 - cyanomethyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole.
Melting point: 143°C.

Example 11

7 - Fluoro - hydroxymethyl - 1,2,3,4 - tetrahydrocarbazole

3.1 grams of 1 - ethoxycarbonyl - 7 - fluoro - 1,2,3,4 - tetrahydrocarbazole were dissolved in 20 ml of absolute ether, and the solution was added dropwise, under nitrogen, to a suspension of 1.5 grams of lithium aluminium hydride in 25 ml of ether. The solution was boiled for a further hour, then cooled, and carefully decomposed with dilute hydrochloric acid. After extraction with ether, the organic phase was dried with magnesium sulphate, and the solution was filtered over a small amount of silica gel. After driving off the solvent, the oily residue was crystallized from a mixture of ether and benzine.

Yield: 63% of 7 - fluoro - 1 - hydroxymethyl - 1,2,3,4 - tetrahydrocarbazole.
Melting point: 83°C.

Example 12

1 - Hydroxymethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried in a manner analogous to that described in Example 11 from 1 - ethoxycarbonyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole in tetrahydrofuran as solvent.

Yield: 80% of the theoretical yield of 1 - hydroxymethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.
Melting point: 98°C.

Example 13

9 - Methyl - 1 - tosyloxymethyl - 1,2,3,4 - tetrahydrocarbazole

7.5 grams of 1 - hydroxymethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole were dissolved in 70 ml of absolute pyridine, and the whole was cooled to −10°C. 8.3 grams of para - toluene sulphochloride were added, and the whole was stirred for 2-1/2 hours. The reaction mixture was diluted with 500 ml of water, and extracted several times with ether. The combined ether extracts were washed first with 2N-hydrochloric acid, then with water, and then dried and concentrated *in vacuo*. The residue was recrystallized from ethanol.

Yield: 83% of the theoretical yield of 9 - methyl - 1 - tosyloxymethyl - 1,2,3,4 - tetrahydrocarbazole.
Melting point: 93°C.

Example 14

1 - Azidomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole

10.7 grams of 9 - methyl - 1 - tosyloxymethyl - 1,2,3,4 - tetrahydrocarbazole were boiled under reflux with 4.7 grams of sodium azide in 100 ml of ethanol and 25 ml of water for 12 hours in an atmosphere of nitrogen. After cooling, the whole was diluted with 150 ml of water and extracted several times with ether.

Yield: 99% of the theoretical yield of 1 - azidomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 72°C.

Example 15

1 - Carbamoyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole

a) 10 grams of 1 - ethoxycarbonyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole in 150 ml of methanol, in which 1 gram of sodium had been dissolved, were saturated with ammonia gas, and agitated in a pressure vessel for 5 days at room temperature. After concentrating, the residue was crystallized from benzene, any ester present remaining in the mother liquor.

Yield: 31% of the theoretical yield of 1 - carbamoyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 197°C.

b) 1.9 grams of 1 - carboxy - 9 - methyl-1,2,3,4 - tetrahydrocarbazole were dissolved in 90 ml of chloroform and the whole was cooled to −10°C. 0.85 gram of triethylamine and 1 gram of chloroformic acid ethyl ester were then added, the mixture was stirred for 30 minutes at 0°C and ammonia was then passed into the solution for 10 minutes, a white precipitate being formed. The mixture was further stirred overnight at room temperature, then thoroughly extracted with chloroform, and the organic phase was washed with water. After removing the solvent, the residue was crystallized from benzene.

Yield: 90% of the theoretical yield of 1 - carbamoyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 199°C.

Example 16

1 - Aminomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole hydrochloride

a) 6.7 grams of 1 - azidomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole in 10 ml of absolute tetrahydrofuran were added dropwise to a suspension of 2.2 grams of lithium aluminium hydride in 100 ml of absolute tetrahydrofuran under nitrogen. The reaction mixture was stirred for 1 hour at room temperature, then cautiously decomposed with a dilute solution of sodium hydroxide, and the organic phase was separated from the inorganic residue. After distilling off the tetrahydrofuran *in vacuo*, the residue was taken up in ether and filtered. After the dropwise addition of a saturated solution of hydrogen chloride gas in ethyl acetate, the hydrochloride of the amine was precipitated, and the latter was filtered off with suction and recrystallized.

Yield: 80% of the theoretical yield of 1 - aminomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole hydrochloride.

Melting point: (Hydrochloride) 249°C (CH_3OH).

b) 2.9 grams of 1 - carboxamido - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole were suspended in 40 ml of absolute tetrahydrofuran, and the whole was added to a suspension of 1.2 grams of lithium aluminum hydride in 40 ml of tetrahydrofuran. The whole was stirred under nitrogen for 30 minutes at room temperature, and was then boiled under reflux for 2 hours. Working up was carried out as described under (a).

Yield: 30% of the theoretical yield of 1 - aminomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: (Hydrochloride) 248°C.

Example 17

1 - Carboxy - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole

5.3 grams of 1 - ethoxycarbonyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole in 10 ml of ethyl alcohol were added to a solution of 22.3 grams of sodium carbonate in 100 ml of water, and the whole was boiled under reflux for 4 hours under nitrogen. The solution was then diluted with 50 ml of water, and, after cooling, was extracted with ether. The aqueous phase was cautiously acidified with hydrochloric acid while cooling with ice, and the resulting precipitate was extracted with ether. After being dried with magnesium sulphate the organic phase was concentrated *in vacuo* at room temperature and crystallized by the addition of cyclohexane.

Yield: 50% of the theoretical yield of 1 - carboxy - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 136°C (ether - cyclo - hexane).

Example 18

1 - Carboxy - 7 - fluoro - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 1 - ethoxycarbonyl - 7 - fluoro - 1,2,3,4 - tetrahydrocarbazole in a manner analogous to that described in Example 17.

Yield: 25% of the theoretical yield of 1 - carboxy - 7 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 106°C (ether - benzine).

Example 19

1 - Carboxy - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 1 - ethoxycarbonyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole in a manner analogous to that described in Example 17.

Yield: 30% of the theoretical yield of 1 - carboxy - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 143°C (ether).

Example 20

1 - Carboxy - 6 - fluoro - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 1 - ethoxycarbonyl - 6 - fluoro - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole in a manner analogous to that described in Example 17.

Yield: 50% of the theoretical yield of 1 - carboxy - 6 - fluoro - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 153°C (ether-cyclohexane).

Example 21

1 - Carboxy - 5 - chloro - 8 - methoxy-1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 1 - ethoxycarbonyl - 5 - chloro - 8 - methoxy-1,2,3,4 - tetrahydrocarbazole in a manner analogous to that described in Example 17.

Yield: 70% of the theoretical yield of 1 - carboxy - 5 - chloro - 8 - methoxy - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 155°C (ether - benzine).

Example 22

1,6 - Dicarboxy - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 1,6 - diethoxycarbonyl - 1,2,3,4 - tetrahydrocarbazole in a manner analogous to that described in Example 17 with the addition of potassium hydroxide. Purification was carried out as follows: the crude acid was dissolved in a mixture of methanol and ether and dicyclohexylamine was added. The resulting salt was recrystallized from a mixture of methanol and ether, and was then decomposed by the addition of 2N - hydrochloric acid.

Yield: 25% of the theoretical yield of 1,6 - dicarboxy - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 194°C.

Example 23

1 - Carboxy - 6,7 - methylenedioxy - 1,2,3,4-tetrahydrocarbazole

The preparation was carried out from 1 - ethoxycarbonyl - 6,7 - methylenedioxy - 1,2,3,4 - tetrahydrocarbazole in a manner analogous to that described in Example 17, and the purification was carried out in a manner analogous to that described in Example 22.

Yield: 25% of the theoretical yield of 1 - carboxy - 6,7 - methylenedioxy - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 128°C (with decomposition).

Example 24

1 - Carboxymethyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole

2 grams of 1 - cyanomethyl - 6 - fluoro-1,2,3,4 - tetrahydrocarbazole were dissolved in 2 ml of dimethyl sulphoxide, and 4.9 grams of potassium hydroxide in 20 ml of water were added. The mixture was heated for 2 hours at 100°C under nitrogen, and was then further stirred for 8 hours at room temperature. The solution was diluted with water and extracted with ethyl acetate. The aqueous phase was cautiously acidified with dilute hydrochloric acid and extracted with methylene chloride.

Yield: 45% of the theoretical yield of oily 1 - carboxymethyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

As the acid does not crystallize, a part of it was converted into the dicyclohexyl - ammonium salt.

Melting point of the salt: 194°C (ethanol).

Example 25

1 - Ethoxycarbonyl - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from aniline and 3 - bromo - 5 - methyl - 2 - oxo - cyclohexane carboxylic acid ethyl ester in a manner analogous to that described in Example 1.

Yield: 74% of the theoretical yield of 1 - ethoxycarbonyl - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 88°C (benzene/methanol).

Example 26

1 - Carboxy - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 1 - ethoxycarbonyl - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole in a manner analogous to that described in Example 17.

Yield: 65% of the theoretical yield of 1 - carboxy - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 126°C (ether/cyclohexane).

Example 27

6 - Fluoro - 1 - hydroxymethyl - 3 - methyl-1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 1 - ethoxycarbonyl - 6 - fluoro - 3 - methyl-1,2,3,4 - tetrahydrocarbazole in a manner analogous to that described in Example 11.

Yield: 75% of the theoretical yield of 6 - fluoro - 1 - hydroxymethyl - 3 - methyl-1,2,3,4 - tetrahydrocarbazole.

Example 28

1 - Ethoxycarbonyl - 5 - chloro - 8 - methyl-1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 3 - bromo - 2 - oxo - cyclohexane carboxylic acid ethyl ester and 5 - chloro - 2 - methyl - aniline in a manner analogous to that described in Example 1 with the addition of zinc chloride.

Yield: 35% of the theoretical yield of 1 - ethoxycarbonyl - 5 - chloro - 8 - methyl-1,2,3,4 - tetrahydrocarbazole.

Melting point: 139°C (benzene).

Example 29

1 - Ethoxycarbonyl - 7 - chloro - 8 - methyl-1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 3 - bromo - 2 - oxo - cyclohexane carboxylic acid ethyl ester and 3 - chloro - 2 - methyl-aniline in a manner analogous to that described in Example 1 with the addition of zinc chloride.

Yield: 40% of the theoretical yield of 1 - ethoxycarbonyl - 7 - chloro - 8 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 141°C (benzene).

Example 30

5 - Chloro - 1 - hydroxymethyl - 8 - methoxy - 1,2,3,4 - tetrahydrocarbazole

The preparation was carried out from 1 - ethoxycarbonyl - 5 - chloro - 8 - methoxy-1,2,3,4 - tetrahydrocarbazole in a manner analogous to that described in Example 11.

Yield: 40% of the theoretical yield of 5 - chloro - 1 - hydroxymethyl - 8 - methoxy-1,2,3,4 - tetrahydrocarbazole.

Melting point: 115°C (ether).

Example 31

1 - Acetamidomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole

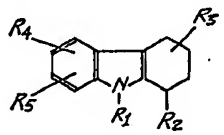
1.4 grams of 1 - aminomethyl - 9 - methyl-1,2,3,4 - tetrahydrocarbazole hydrochloride were suspended in 50 ml of ether, and treated with a dilute solution of sodium carbonate. The organic phase was separated off and dried with potassium carbonate, and the solvent was removed. The residue was dissolved in 10 ml of pyridine (absolute) and 0.5 gram of acetyl chloride was added at 0°C. The mixture was stirred for 1 hour, then diluted with water and extracted with ether. The ether phase was first washed with dilute hydrochloric acid and then with water, dried over magnesium sulphate, and concentrated. The residue was recrystallized from a mixture of methanol and water.

Yield: 40% of the theoretical yield of 1 - acetamidomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

Melting point: 164°C.

WHAT WE CLAIM IS:—

1. A compound of the general formula I



(I)

in which

R_1 represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms,

R_2 represents a hydroxyalkyl, aminoalkyl, acetamidoalkyl, azidoalkyl or tosyloxyalkyl group containing 1 to 4 carbon atoms in the alkyl group and, when R_1, R_3, R_4 and R_5 are not all simultaneously hydrogen atoms, may also represent a group of the general formula

$$-(CH_2)_n-X,$$

in which n represents 0 or 1 and X represents a carboxyl, alkoxycarbonyl, carbamoyl or nitrile group,

R_3 represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms, and

R_4 represents a hydrogen or fluorine atom, an alkyl group containing 2 to 6 carbon atoms, a trifluoromethyl group, an alkoxy group containing 3 to 6 carbon atoms, or a nitro, carboxyl, amino, hydroxyl or nitrile group and, when R_5 does not represent a hydrogen atom, may also represent a chlorine atom, and

R_5 represents in the 5-, 7- or 8-position a hydrogen atom, a halogen atom, an alkyl group containing 1 to 4 carbon atoms or an alkoxy group containing 1 to 6 carbon atoms, or

R_4 and R_5 together represent a 6,7 - methylenedioxy group, or an enantiomer thereof.

2. A salt of a compound as claimed in claim 1 capable of forming a salt.

3. A physiologically tolerable salt of a compound as claimed in claim 1 capable of forming a salt.

4. 1 - Ethoxycarbonyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

5. 1 - Ethoxycarbonyl - 6 - trifluoromethyl-1,2,3,4 - tetrahydrocarbazole.

6. 1 - Ethoxycarbonyl - 6 - *n* - butyl - 1,2,3,4 - tetrahydrocarbazole.

7. 1 - Ethoxycarbonyl - 6 - nitro - 1,2,3,4 - tetrahydrocarbazole.

8. 1 - Ethoxycarbonyl - 7 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

9. 1 - Ethoxycarbonyl - 5 - chloro - 8 - methoxy - 1,2,3,4 - tetrahydrocarbazole.

10. 1 - Ethoxycarbonyl - 6,7 - methylenedioxy - 1,2,3,4 - tetrahydrocarbazole.

11. 1 - Ethoxycarbonyl - 6 - fluoro - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole.

12. 1 - Ethoxycarbonyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

13. 1 - Cyanomethyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

14. 1 - Hydroxymethyl - 7 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

15. 1 - Hydroxymethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

16. 1 - Tosyloxymethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

17. 1 - Azidomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

18. 1 - Aminomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole hydrochloride.

19. 1 - Carbamoyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

20. 1 - Carboxy - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

21. 1 - Carboxy - 7 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

22. 1 - Carboxy - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

23. 1 - Carboxy - 6 - fluoro - 3 - methyl-1,2,3,4 - tetrahydrocarbazole.

24. 1 - Carboxy - 5 - chloro - 8 - methoxy - 1,2,3,4 - tetrahydrocarbazole.

25. 1,6 - Dicarboxy - 1,2,3,4 - tetrahydrocarbazole.

26. 1 - Carboxy - 6,7 - methylenedioxy - 1,2,3,4 - tetrahydrocarbazole.

27. 1 - Carboxymethyl - 6 - fluoro - 1,2,3,4 - tetrahydrocarbazole.

28. 1 - Ethoxycarbonyl - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole.

29. 1 - Carboxy - 3 - methyl - 1,2,3,4 - tetrahydrocarbozole.

30. 6 - Fluoro - 1 - hydroxymethyl - 3 - methyl - 1,2,3,4 - tetrahydrocarbazole.

31. 1 - Ethoxycarbonyl - 5 - chloro - 8 - methyl - 1,2,3,4 - tetrahydrocarbazole.

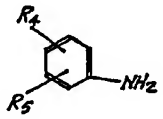
32. 1 - Ethoxycarbonyl - 7 - chloro - 8 - methyl - 1,2,3,4 - tetrahydrocarbazole.

33. 5 - Chloro - 1 - hydroxymethyl - 8 - methoxy - 1,2,3,4 - tetrahydrocarbazole.

34. 1 - Acetamidomethyl - 9 - methyl - 1,2,3,4 - tetrahydrocarbazole.

35. A process for the manufacture of a compound as claimed in claim 1 or a salt of such a compound capable of forming a salt, wherein

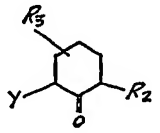
a) a substituted aniline of the general formula II



(II),

in which

R_4 and R_5 have the meanings given in claim 1, or a salt thereof, is reacted with a cyclohexanone derivative of the general formula III



(III),

in which

R_2 represents a

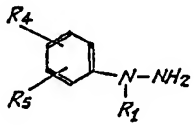
$$-(CH_2)_n-X$$

group in which n and X have the meanings given in claim 1,

Y represents a halogen atom, and

R_3 has the meaning given in claim 1, and if desired, the resulting compound is alkylated at the nitrogen atom to form a compound in which R_1 represents an alkyl group containing 1 to 4 carbon atoms, or

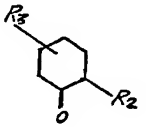
b) an N_1-substituted phenyl - hydrazine of the general formula IV



(IV),

in which

R_1, R_4 and R_5 have the meanings given in claim 1, or a salt thereof, is reacted with a cyclohexanone derivative of the general formula V



(V),

in which

R_2 and R_3 have the meanings given in claim 1, and, if desired, any resulting acid derivative obtained according to method (a) or (b) is hydrolysed and/or any resulting free 1 - carboxylic acid is converted into an ester thereof, and/or, if desired, any resulting ester is either (i) converted into a carbamoyl compound and then, if desired, the carbamoyl compound is reduced to an aminoalkyl compound or (ii) reduced to a hydroxyalkyl compound, the hydroxyalkyl compound is then, if desired, converted into the tosylate, the tosylate is then, if desired, converted into an azidoalkyl compound and the azidoalkyl compound is, if desired, reduced to an aminoalkyl compound, and/or, if desired, any resulting compound capable of forming a salt is converted into a salt thereof and/or any resulting salt is converted into the corresponding free compound.

36. A process as claimed in claim 35, wherein Y represents a bromine atom.

37. A process for the manufacture of a compound as claimed in claim 1 or 2, conducted substantially as described in any one of Examples 1 to 27 herein.

38. A process for the manufacture of a compound as claimed in claim 1, conducted substantially as described in any one of Examples 28 to 31 herein.

39. A pharmaceutical preparation which comprises a compound as claimed in claim 1, in admixture or conjunction with a pharmaceutically suitable carrier.

40. A pharmaceutical preparation which comprises a salt as claimed in claim 3, in admixture or conjunction with a pharmaceutically suitable carrier.

41. A pharmaceutical preparation which comprises the compound claimed in any one of claims 4 to 34, in admixture or conjunction with a pharmaceutically suitable carrier.

42. A pharmaceutical preparation as claimed in any one of claims 39 to 41, which is in the form of a tablet, dragrée, capsule or pill.

43. A pharmaceutical preparation as claimed in any one of claims 39 to 41, which is in the form of a suspension or solution.

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